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In Figures 2, 3, and 4, numeric city-specific hazard ratios and 95% confidence intervals were for a 5-μg/m^3 increase in $PM_{2.5}$, whereas the plotted values were for a 1-μg/m^3 increase as indicated in the figure legends. Revised Figures 2, 3, and 4 are shown below and contain numeric values that correspond to a 1-μg/m^3 increase. The authors regret these errors.

Figure 2.

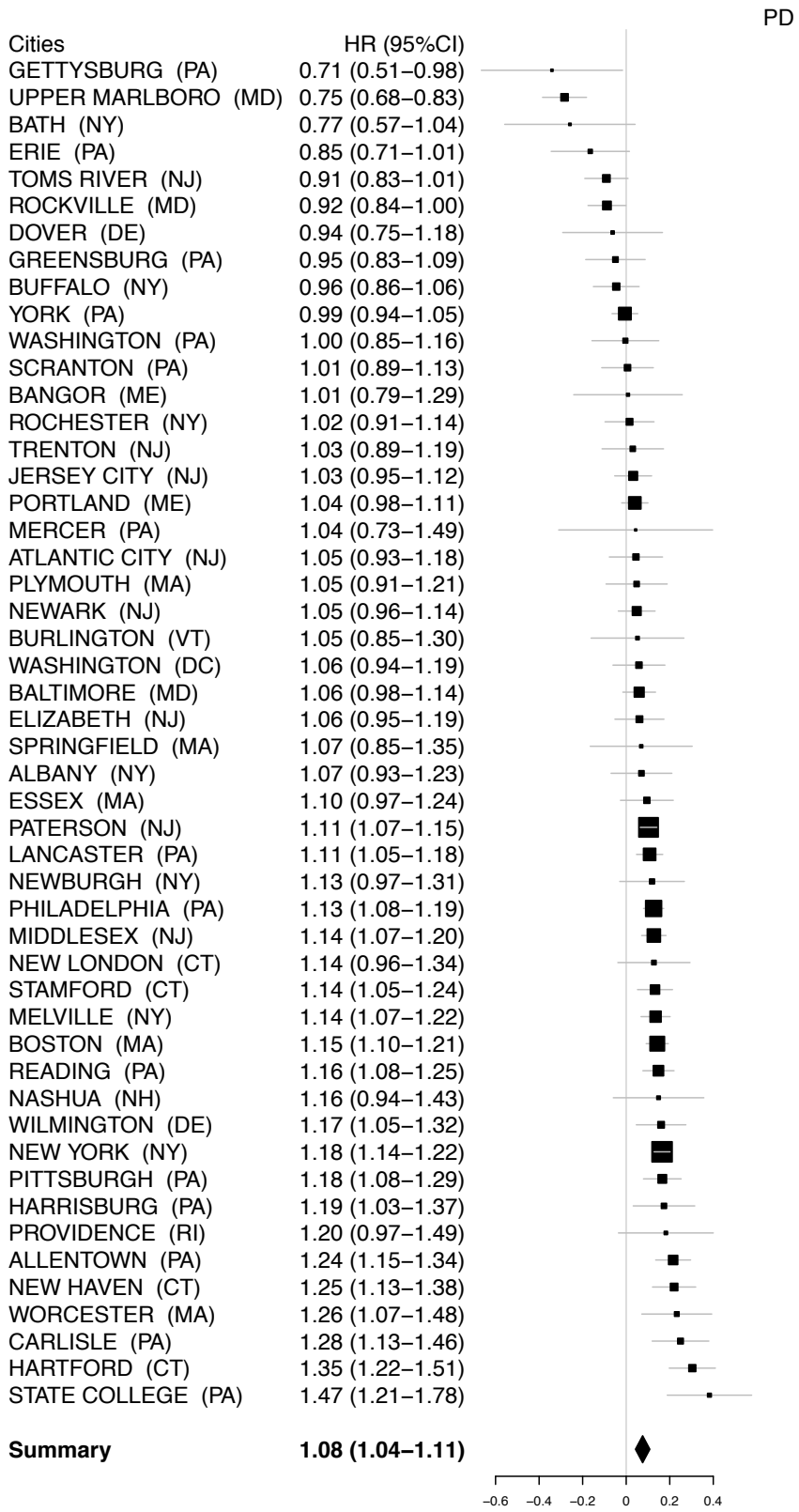

PD
Cities
HR (95%CI)
GETTYSBURG (PA) 0.71 (0.51–0.98)
UPPER MARLBORO (MD) 0.75 (0.68–0.83)
BATH (NY) 0.77 (0.57–1.04)
ERIE (PA) 0.85 (0.71–1.01)
TOMS RIVER (NJ) 0.91 (0.83–1.01)
ROCKVILLE (MD) 0.92 (0.84–1.00)
DOVER (DE) 0.94 (0.75–1.18)
GREENSBURG (PA) 0.95 (0.83–1.09)
BUFFALO (NY) 0.96 (0.86–1.06)
YORK (PA) 0.99 (0.94–1.05)
WASHINGTON (PA) 1.00 (0.85–1.16)
SCRANTON (PA) 1.01 (0.89–1.13)
BANGOR (ME) 1.01 (0.79–1.29)
ROCHESTER (NY) 1.02 (0.91–1.14)
TRENTON (NJ) 1.03 (0.89–1.19)
JERSEY CITY (NJ) 1.03 (0.95–1.12)
PORTLAND (ME) 1.04 (0.98–1.11)
MERCER (PA) 1.04 (0.73–1.49)
ATLANTIC CITY (NJ) 1.05 (0.93–1.18)
PLYMOUTH (MA) 1.05 (0.91–1.21)
NEWARK (NJ) 1.05 (0.96–1.14)
BURLINGTON (VT) 1.05 (0.85–1.30)
WASHINGTON (DC) 1.06 (0.94–1.19)
BALTIMORE (MD) 1.06 (0.98–1.14)
ELIZABETH (NJ) 1.06 (0.95–1.19)
SPRINGFIELD (MA) 1.07 (0.85–1.35)
ALBANY (NY) 1.07 (0.93–1.23)
ESSEX (MA) 1.10 (0.97–1.24)
PATERSON (NJ) 1.11 (1.07–1.15)
LANCASTER (PA) 1.11 (1.05–1.18)
NEWBURGH (NY) 1.13 (0.97–1.31)
PHILADELPHIA (PA) 1.13 (1.08–1.19)
MIDDLESEX (NJ) 1.14 (1.07–1.20)
NEW LONDON (CT) 1.14 (0.96–1.34)
STAMFORD (CT) 1.14 (1.05–1.24)
MELVILLE (NY) 1.14 (1.07–1.22)
BOSTON (MA) 1.15 (1.10–1.21)
READING (PA) 1.16 (1.08–1.25)
NASHUA (NH) 1.16 (0.94–1.43)
WILMINGTON (DE) 1.17 (1.05–1.32)
NEW YORK (NY) 1.18 (1.14–1.22)
PITTSBURGH (PA) 1.18 (1.08–1.29)
HARRISBURG (PA) 1.19 (1.03–1.37)
PROVIDENCE (RI) 1.20 (0.97–1.49)
ALLENTOWN (PA) 1.24 (1.15–1.34)
NEW HAVEN (CT) 1.25 (1.13–1.38)
WORCESTER (MA) 1.26 (1.07–1.48)
CARLISLE (PA) 1.28 (1.13–1.46)
HARTFORD (CT) 1.35 (1.22–1.51)
STATE COLLEGE (PA) 1.47 (1.21–1.78)
Summary 1.08 (1.04–1.11)
−0.6 −0.4 −0.2 0 0.2 0.4

Figure 3.

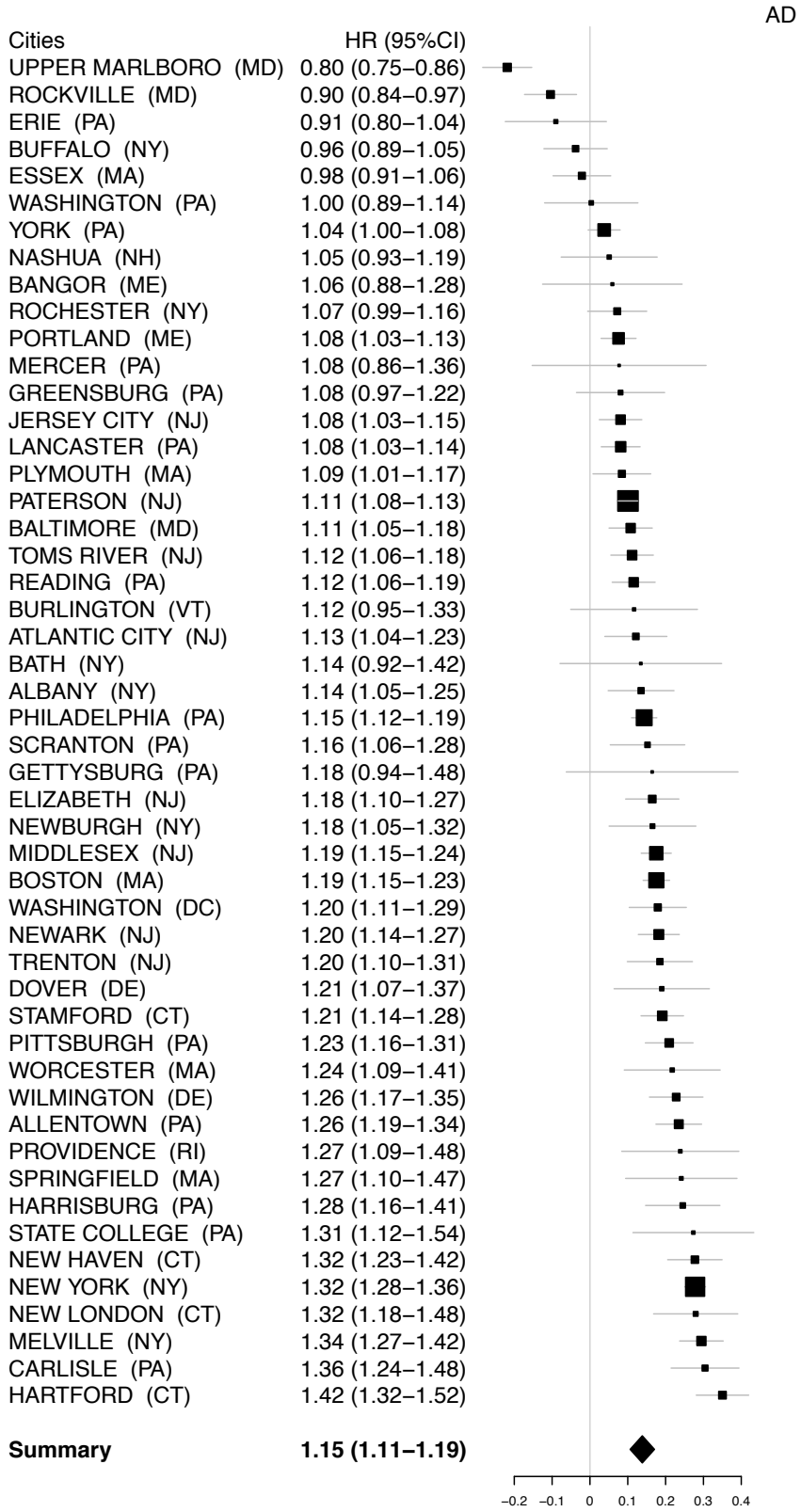
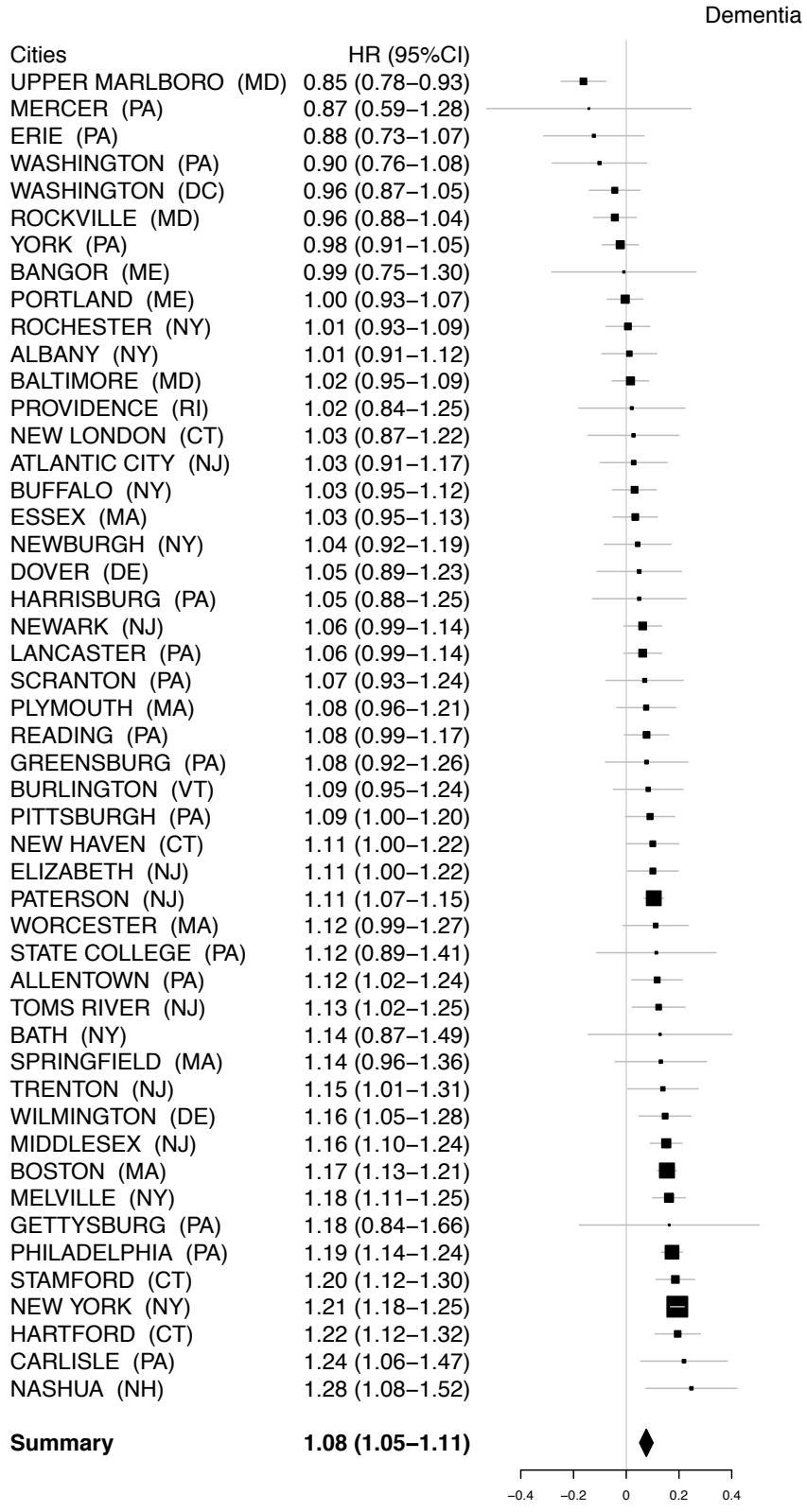

AD
Cities
HR (95%CI)
UPPER MARLBORO (MD) 0.80 (0.75–0.86)
ROCKVILLE (MD) 0.90 (0.84–0.97)
ERIE (PA) 0.91 (0.80–1.04)
BUFFALO (NY) 0.96 (0.89–1.05)
ESSEX (MA) 0.98 (0.91–1.06)
WASHINGTON (PA) 1.00 (0.89–1.14)
YORK (PA) 1.04 (1.00–1.08)
NASHUA (NH) 1.05 (0.93–1.19)
BANGOR (ME) 1.06 (0.88–1.28)
ROCHESTER (NY) 1.07 (0.99–1.16)
PORTLAND (ME) 1.08 (1.03–1.13)
MERCER (PA) 1.08 (0.86–1.36)
GREENSBURG (PA) 1.08 (0.97–1.22)
JERSEY CITY (NJ) 1.08 (1.03–1.15)
LANCASTER (PA) 1.08 (1.03–1.14)
PLYMOUTH (MA) 1.09 (1.01–1.17)
PATERSON (NJ) 1.11 (1.08–1.13)
BALTIMORE (MD) 1.11 (1.05–1.18)
TOMS RIVER (NJ) 1.12 (1.06–1.18)
READING (PA) 1.12 (1.06–1.19)
BURLINGTON (VT) 1.12 (0.95–1.33)
ATLANTIC CITY (NJ) 1.13 (1.04–1.23)
BATH (NY) 1.14 (0.92–1.42)
ALBANY (NY) 1.14 (1.05–1.25)
PHILADELPHIA (PA) 1.15 (1.12–1.19)
SCRANTON (PA) 1.16 (1.06–1.28)
GETTYSBURG (PA) 1.18 (0.94–1.48)
ELIZABETH (NJ) 1.18 (1.10–1.27)
NEWBURGH (NY) 1.18 (1.05–1.32)
MIDDLESEX (NJ) 1.19 (1.15–1.24)
BOSTON (MA) 1.19 (1.15–1.23)
WASHINGTON (DC) 1.20 (1.11–1.29)
NEWARK (NJ) 1.20 (1.14–1.27)
TRENTON (NJ) 1.20 (1.10–1.31)
DOVER (DE) 1.21 (1.07–1.37)
STAMFORD (CT) 1.21 (1.14–1.28)
PITTSBURGH (PA) 1.23 (1.16–1.31)
WORCESTER (MA) 1.24 (1.09–1.41)
WILMINGTON (DE) 1.26 (1.17–1.35)
ALLENTOWN (PA) 1.26 (1.19–1.34)
PROVIDENCE (RI) 1.27 (1.09–1.48)
SPRINGFIELD (MA) 1.27 (1.10–1.47)
HARRISBURG (PA) 1.28 (1.16–1.41)
STATE COLLEGE (PA) 1.31 (1.12–1.54)
NEW HAVEN (CT) 1.32 (1.23–1.42)
NEW YORK (NY) 1.32 (1.28–1.36)
NEW LONDON (CT) 1.32 (1.18–1.48)
MELVILLE (NY) 1.34 (1.27–1.42)
CARLISLE (PA) 1.36 (1.24–1.48)
HARTFORD (CT) 1.42 (1.32–1.52)
Summary 1.15 (1.11–1.19)
−0.2 −0.1 0 0.1 0.2 0.3 0.4

Figure 4.


Dementia
Cities
HR (95%CI)
UPPER MARLBORO (MD) 0.85 (0.78–0.93)
MERCER (PA) 0.87 (0.59–1.28)
ERIE (PA) 0.88 (0.73–1.07)
WASHINGTON (PA) 0.90 (0.76–1.08)
WASHINGTON (DC) 0.96 (0.87–1.05)
ROCKVILLE (MD) 0.96 (0.88–1.04)
YORK (PA) 0.98 (0.91–1.05)
BANGOR (ME) 0.99 (0.75–1.30)
PORTLAND (ME) 1.00 (0.93–1.07)
ROCHESTER (NY) 1.01 (0.93–1.09)
ALBANY (NY) 1.01 (0.91–1.12)
BALTIMORE (MD) 1.02 (0.95–1.09)
PROVIDENCE (RI) 1.02 (0.84–1.25)
NEW LONDON (CT) 1.03 (0.87–1.22)
ATLANTIC CITY (NJ) 1.03 (0.91–1.17)
BUFFALO (NY) 1.03 (0.95–1.12)
ESSEX (MA) 1.03 (0.95–1.13)
NEWBURGH (NY) 1.04 (0.92–1.19)
DOVER (DE) 1.05 (0.89–1.23)
HARRISBURG (PA) 1.05 (0.88–1.25)
NEWARK (NJ) 1.06 (0.99–1.14)
LANCASTER (PA) 1.06 (0.99–1.14)
SCRANTON (PA) 1.07 (0.93–1.24)
PLYMOUTH (MA) 1.08 (0.96–1.21)
READING (PA) 1.08 (0.99–1.17)
GREENSBURG (PA) 1.08 (0.92–1.26)
BURLINGTON (VT) 1.09 (0.95–1.24)
PITTSBURGH (PA) 1.09 (1.00–1.20)
NEW HAVEN (CT) 1.11 (1.00–1.22)
ELIZABETH (NJ) 1.11 (1.00–1.22)
PATERSON (NJ) 1.11 (1.07–1.15)
WORCESTER (MA) 1.12 (0.99–1.27)
STATE COLLEGE (PA) 1.12 (0.89–1.41)
ALLENTOWN (PA) 1.12 (1.02–1.24)
TOMS RIVER (NJ) 1.13 (1.02–1.25)
BATH (NY) 1.14 (0.87–1.49)
SPRINGFIELD (MA) 1.14 (0.96–1.36)
TRENTON (NJ) 1.15 (1.01–1.31)
WILMINGTON (DE) 1.16 (1.05–1.28)
MIDDLESEX (NJ) 1.16 (1.10–1.24)
BOSTON (MA) 1.17 (1.13–1.21)
MELVILLE (NY) 1.18 (1.11–1.25)
GETTYSBURG (PA) 1.18 (0.84–1.66)
PHILADELPHIA (PA) 1.19 (1.14–1.24)
STAMFORD (CT) 1.20 (1.12–1.30)
NEW YORK (NY) 1.21 (1.18–1.25)
HARTFORD (CT) 1.22 (1.12–1.32)
CARLISLE (PA) 1.24 (1.06–1.47)
NASHUA (NH) 1.28 (1.08–1.52)
Summary 1.08 (1.05–1.11)
−0.4
−0.2
0
0.2
0.4

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Long-term $PM_{2.5}$ Exposure and Neurological Hospital Admissions in the Northeastern United States

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Running head: Long-term $PM_{2.5}$ and neurological admissions

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Competing financial interests: The authors declare no conflict of interest.

Abstract

Background: Long-term exposure to fine particles ($PM_{2.5}$) has been consistently linked to heart and lung disease. Recently there has been increased interest to examine the effects of air pollution on the nervous system, with evidence showing potentially harmful effects on neurodegeneration. Our objective was to assess the potential impact of long-term $PM_{2.5}$ exposure on event time, defined as time to the first admission for dementia, Alzheimer's or Parkinson's diseases (AD and PD, respectively) in an elderly population across the Northeastern US.

Methods: We estimated the effects of $PM_{2.5}$ on first hospital admission for dementia, AD and PD, among all Medicare enrollees >64 years in 50 northeastern US cities (1999–2010). For each outcome, we first ran a Cox proportional hazards model in each city, adjusting for prior cardiopulmonary-related hospitalizations and year, and stratified by follow-up time, age, gender and race. We then pooled the city-specific estimates together by employing a random effects meta-regression.

Results: We followed approximately 10 million subjects and observed significant associations of long-term $PM_{2.5}$ city-wide exposure on all three outcomes. Specifically, we estimated a HR of 1.08; 95% CI: 1.05, 1.11 for dementia, 1.15; 95% CI: 1.11, 1.19 for AD and 1.08; 95% CI: 1.04, 1.12 for PD admissions per 1 $\mu g/m^3$ of increase in annual $PM_{2.5}$ concentrations.

Conclusions: To our knowledge, this is the first study to examine the relationship between long-term exposure to $PM_{2.5}$ and time to the first hospitalization for the most common neurodegenerative diseases. We found strong evidence of an association for all three outcomes. Our findings provide the basis for more studies, as the implications to public health can be crucial.

Introduction

Long-term exposure to $PM_{2.5}$, particles with aerodynamic diameter ≥2.5 μm, has been consistently associated with a series of outcomes, including, but not limited to, mortality (Krewski et al. 2009), cardiovascular (Puett et al. 2009), and cerebrovascular events (Stafoggia et al. 2014), and lung cancer (Hamra et al. 2014).

Recently, there has been an increased interest in the effects of air pollution on the central nervous system (CNS) and neurodegeneration. Particle exposures have been associated with decreased cognitive function (Power et al. 2011), faster cognitive decline (Weuve et al. 2012), and Parkinson's disease (PD) hospitalizations (Zanobetti et al. 2014). Toxicological studies provide further evidence of an association between particulate air pollution and neurodegeneration, highlighting potential biological pathways, including systemic inflammation (Block et al. 2007, 2012), which has also been consistently linked with particle exposures (Madrigano et al. 2009; Rückerl et al. 2006). Based on their findings on the effects of air pollution on neuroinflammation, in particular, and altered brain innate immune response, Calderón-Garcidueñas et al. (2008b) urged that air pollution should be considered a risk factor for both Alzheimer's and Parkinson's Diseases (AD and PD, respectively).

AD and PD are the two most prevalent neurodegenerative diseases (Maragakis and Rothstein 2006). AD is the most common form of dementia (Blennow et al. 2006); in 2013 an estimated 5.2 million Americans had AD and between 1999 and 2010 the proportion of deaths resulting from AD in the US increased by 68% (Thies et al. 2013). PD is the most common serious movement disorder in the world (Samii et al. 2004), with an estimated age- and gender-adjusted incidence rate of 13.4 per 100,000 person years (Van Den Eeden et al. 2003). Tschanz et al.

(2011) reported that the progression of disease is slow for a significant proportion of patients with neurodegenerative diseases, and AD specifically, and urged for identification of modifiable factors that may further slow the neurodegenerative progression.

The association between long-term exposure to ambient air pollution and PD and AD has not been explored in large-scale epidemiologic studies, with the exception of three studies that examined the relation of airborne metal exposures and PD, showing suggestive evidence of harmful manganese (Finkelstein and Jerrett 2007; Willis et al. 2010) and mercury effects (Palacios et al. 2014). Moreover, while there is some evidence that air pollution may be involved in initiation of neurodegeneration (Calderón-Garcidueñas et al. 2008a, 2013), we propose that it might also be involved in disease progression, potentially by worsening of intermediate processes, such as oxidative stress, systemic inflammation and neuroinflammation, and accelerating, through these pathways, the occurrence of first hospital admission. Holmes et al. (2009), for instance, reported that both acute and chronic systemic inflammation is associated with an increase in cognitive decline among early AD patients.

With this study, we investigated the effect of long-term exposure to $PM_{2.5}$ on event time, defined as time of the first hospital admission for PD, AD or dementia in an elderly population across the Northeastern US. Specifically, we investigated whether $PM_{2.5}$ city-wide exposures are associated with accelerated disease progression, leading to the first hospital admission. To do so we used data from approximately 10 million Medicare enrollees residing in 50 cities in the Northeastern US, between 1999 and 2010. We used a recently published statistical approach (Kioumourtzoglou et al. 2014a), that was previously used to assess whether yearly fluctuations in $PM_{2.5}$ concentrations are associated with yearly fluctuations in mortality. For the present study,

we applied the same approach to assess associations with yearly fluctuations in the time of first hospitalization for each of the three outcomes of interest. Our proposed approach effectively randomizes our exposure with respect to most plausible covariates, by eliminating potential confounding by factors varying across cities and long-term trends.

Methods

Data collection

Study Population. Data were obtained from approximately 10 million fee-for-service Medicare enrollees (>64 years old) from 50 cities across the Northeastern US, specifically from the states CT, DE, DC, ME, MD, MA, NH, NJ, NY, PA, RI, and VT, for the years 1999–2010. Enrollment records were obtained from the Center for Medicaid and Medicare (CMS) (Dominici et al. 2006; Greven et al. 2011; Zeger et al. 2008). These states and cities were chosen due to data availability and also because researchers have observed higher effect estimates of $PM_{2.5}$ in the Northeast, compared to other US regions, for other outcomes, such as mortality (Zanobetti and Schwartz 2009; Zeger et al. 2008) and cardiovascular mortality (Puett et al. 2009). A map of the location of the 50 cities included in our analyses is presented in Figure 1. This study was conducted under a protocol approved by the Harvard School of Public Health Human Subjects Committee.

Medicare is an open cohort; subjects entered our cohort in 1999, or upon their enrollment after 1999 (when they turn 65). For each enrollee, a record was created for each year of follow-up, which started on January 1st following entry into the cohort, and each subject was followed over time until the event (first admission for any of the outcomes of interest), or until the year of their death or the end of our study period (December 2010).

We also obtained date and primary and secondary diagnoses for each admission, which were linked to the annual records using the unique IDs of each enrollee. Specifically, using codes from the *International Classification of Diseases, 9th Revision Clinical Modification* (ICD-9; Center for Disease Control and Prevention 2008), we obtained admission records for PD (code 332), AD (code 331.0) and dementia (code 290), congestive heart failure (CHF; code 428), myocardial infarction (MI; code 410), chronic obstructive pulmonary disease (COPD; codes 490–492, 494–496), and diabetes (code 250), as well as severity of each admission, expressed by the number of days spent in the coronary or intensive care units.

Individual-level information was available for cause-specific admissions, gender, age, race and zip code of residence. Information on individual level risk factors, such as individual socioeconomic status (SES), smoking and diet, is not available for Medicare enrollees. As a proxy for SES, we used zip-code level median income, obtained from the 2000 U.S. Census Bureau (Census 2000).

Air pollution data. We obtained $PM_{2.5}$ data from the US Environmental Protection Agency's (EPA) Air Quality System (AQS) database (US EPA 2013). We estimated annual $PM_{2.5}$ averages within each city for 1999–2010. If multiple monitors were available in a city, we used the average of all monitors. Within cities and for each follow-up year, each participant was assigned annual (January 1st–December 31st) city-average $PM_{2.5}$ mass concentrations as a time-varying exposure.

Data Analysis

Health Models. We ran separate models for each outcome of interest, i.e. PD, AD and dementia, using the first available, either primary or secondary, hospitalization for these conditions. We fit

time-varying Cox proportional hazards models separately in each city. City-wide annual $PM_{2.5}$ concentrations were included as the time-varying exposure of interest, as well as a term for calendar year (linear). We employed the counting process extension of the model by Andersen and Gill (Andersen and Gill 1982), to create multiple observations per subject, with each observation representing a single person-year of follow-up.

We fit city-specific models to avoid confounding by factors that vary across cities. By also adjusting for calendar year, we estimated whether year-to-year variations in $PM_{2.5}$ concentrations around their long-term city-specific trends are related to year-to-year variations in cause-specific admissions in each city. With this approach, we eliminated all confounding by covariates that vary across cities, since this is a city-specific analysis, and by covariates whose long-term trends coincide with trends in $PM_{2.5}$ within cities, since those trends are removed. We assume year-to-year differences in $PM_{2.5}$ concentrations around their city-specific trends to be driven by year-to-year variations in the percent of time the city was downwind from higher or lower polluted areas, and year-to-year variations in wind speed and inversions. Long-term changes in other exposures, such as e.g. changes in smoking rates and socioeconomic status, should be captured in the long-term trends, for which we adjust. We think it is implausible that e.g. year-to-year variations in smoking rates around their long-term trend within city are correlated with year-to-year fluctuations in pollution concentrations driven by back trajectories etc. Assuming this is true, our exposure variations are random with respect to other risk factors for admissions, and hence our models should provide an unbiased estimate of the effects of $PM_{2.5}$.

We, moreover, adjusted for any previous admission for CHF, COPD, MI or diabetes and number of days spent in the intensive and coronary care units. We also adjusted for zip-code level

median income, as a proxy for SES. All models were stratified by age (in 1-year intervals), gender, race (as white, black and other) and year of follow up.

City-specific effect estimates were then pooled together in a second stage, using a random effects meta-analysis (Berkey et al. 1998; Riley et al. 2011). We, thus, present in the Results section the pooled estimates for each outcome, as hazard ratios (HR) per 1 $\mu g/m^3$ increase in $PM_{2.5}$.

Further, we assessed potential effect modification by gender. In the city-specific models (first stage) we included an interaction term between $PM_{2.5}$ concentrations and gender. We then pooled the city-specific coefficients of the interaction terms in a random effects meta-analysis and assessed whether the pooled effect estimate was statistically different than zero at the 0.05 level.

Finally, to assess whether the association between $PM_{2.5}$ and neurological admissions is nonlinear, we repeated our main analysis using $PM_{2.5}$ quartiles as a categorical variable.

For our statistical analyses we used the SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA), and the R Statistical Software, version 2.14.1 (Foundation for Statistical Computing, Vienna, Austria).

Sensitivity Analyses. To assess the robustness of our findings, we conducted two sensitivity analyses, following the same methods as in the main analyses. First, given that one of the suggested biological pathways for $PM_{2.5}$ effects on neurodegeneration is through inflammation (Block et al. 2007), adjusting for prior admissions for cardiovascular causes, i.e. MI and CHF, might mean that we have adjusted for a proxy for a potential mediator (inflammation). To investigate this further, we repeated analyses without adjusting for prior MI and CHF hospitalizations.

Moreover, since Medicare enrollees enter our cohort at the age of 65, there is no information on whether they had been hospitalized for any of the outcomes of interest at a younger age. To address this further, in an effort to remove potentially prevalent cases, we repeated our analyses, removing subjects that had been hospitalized for these outcomes during their first two years of follow up and following the remaining participants from the third year of follow up onwards.

Results

We included data from 50 cities in our analyses. The number of subjects and cause-specific admissions are presented in Table 1. Overall, our cohort consisted of more than 9 million subjects and in total we observed 119,425 first PD, 266,725 AD and 203,463 dementia admissions (either as primary or secondary causes). Across cities, the mean age in our cohort was 75.6 years (SD: 7.6), 57.3% of the subjects were female and 80.4% white. The average $PM_{2.5}$ concentration was 12.0 $\mu g/m^3$ (SD=1.6, IQR = 3.8 $\mu g/m^3$).

City-specific estimates are presented in Figures 2–4. Overall, we observed statistically significant, positive pooled effect estimates of $PM_{2.5}$ concentrations on all three outcomes of interest. Specifically, we observed a HR = 1.08; 95%CI: 1.04,1.12 for PD, 1.15; 95%CI: 1.11, 1.19 for AD and 1.08; 95%CI: 1.05, 1.11 for dementia admissions, per 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ city-wide exposures. We detected significant heterogeneity in the estimates across cities for all outcomes ($p < 0.001$).

For comparability with other long-term $PM_{2.5}$ studies (e.g. Beelen et al. 2014) we also present our results per 5 $\mu g/m^3$ (Table 1). We found no evidence of a non-linear relationship as all observed associations by quartiles were monotonically increasing (results not shown).

We observed no statistically significant effect modification by gender for any outcome (all interaction $p > 0.05$) (data not shown). We found the largest by-gender difference across the estimated HRs for AD admissions, with HR = 1.16; 95%CI: 1.12, 1.21 for men and 1.14; 95%CI: 1.10, 1.18 for women (p-interaction = 0.58).

Sensitivity Analyses

Our estimated HRs did not change when we repeated analyses excluding any prior MI or CHF admission as variables from our first-stage model (results not shown).

The number of subjects and outcome-specific admissions when we excluded potentially prevalent cases are presented in Table 1. The estimated HRs in this sensitivity analyses were very similar to the HRs estimated in the main analysis.

Discussion

We conducted a large-scale, multi-city study to estimate the impact of long-term $PM_{2.5}$ city-wide exposures on city-wide hospital admissions for neurological outcomes, using data from Medicare enrollees in the Northeastern US. We followed almost 10 million subjects from 1999 to 2010 and observed statistically significant, positive associations for all three outcomes of interest: first admission for PD, AD and dementia. Our results were robust to the sensitivity analyses we conducted.

Although some published studies have reported positive associations between $PM_{2.5}$ and reduced cognitive function (Gatto et al. 2014; Ranft et al. 2009), no epidemiologic studies have investigated the effect of long-term $PM_{2.5}$ on PD and AD. Recently, in an analysis of short-term $PM_{2.5}$ effects, Zanobetti et al. (2014) reported a significant increase in PD-related

hospitalizations after increased 2-day $PM_{2.5}$ exposures. Only a few studies have examined the impact of long-term exposure to airborne metals on PD. Urban $PM_{2.5}$ contain metals (Seinfeld and Pandis 2006), with the $PM_{2.5}$ metal concentrations depending on the $PM_{2.5}$ sources in each city (Kioumourtzoglou et al. 2014b; Lall et al. 2011). Finkelstein and Jerrett (2007) observed increased odds ratios for a physician diagnosis of PD after exposure to particulate manganese. Similarly, Willis et al. (2010), using Medicare data, found increased incidence rates of PD among subjects living in counties with high reported industrial release of manganese or copper. Palacios et al. (2014), finally, reported elevated, albeit not statistically significant, associations between airborne mercury levels and PD in a cohort of elderly women.

Even though the direct epidemiologic evidence linking $PM_{2.5}$ exposures to neurodegenerative diseases is sparse, toxicological studies have been published proposing several potential biological pathways (Block and Calderón-Garcidueñas 2009; Block et al. 2012). One potential pathway, for instance, is through oxidative stress: air pollution exposures have been repeatedly linked to oxidative stress (Chuang et al. 2007; Kim et al. 2004; Li et al.2003; Sørensen et al. 2003). Several studies, furthermore, reported evidence suggesting that oxidative stress plays a key pathogenic role in AD (Bonda et al. 2010; Huang et al. 2004; Su et al. 2008; Zhu et al. 2004). Inflammation has also been related to both air pollution exposures and neurodegeneration (Block and Calderón-Garcidueñas 2009). Both short- and long-term exposures to $PM_{2.5}$ have been linked to increases in blood inflammatory markers (Dubowsky et al. 2006; Hoffmann et al. 2009). Inflammatory processes are thought to play an important role both in PD (McGeer and McGeer 2004), and AD pathogenesis (Wyss-Coray 2006).

Given the design of our study and the use of administrative data, we were not able to assess

whether air pollution is associated with onset of neurodegeneration. Rather, we assessed whether year-to-year fluctuations in $PM_{2.5}$ concentrations are associated with increases in hospital admissions for neurologic disorders. Our findings, thus, indicate that air pollution likely accelerates the progression of neurodegeneration, potentially after onset of disease.

The role of inflammation on progression of neurodegeneration has been consistently reported (Cunningham et al. 2005; Teeling and Perry 2009). Cunningham et al. (2009) reported that inflammation primes the brain, making it more vulnerable to future inflammatory insults, which in turn changes the rate of neurodegeneration and accelerates disease progression. Furthermore, increased exposures to $PM_{2.5}$ in general, or traffic particles specifically, have been associated with a series of intermediate outcomes, which in turn have been linked to more rapid cognitive decline or acceleration of AD progression, such as increased blood homocysteine (Oulhaj et al. 2010; Qiao et al. 2014; Ren et al. 2010), increased hypertension (Foraster et al. 2014; Goldstein et al. 2013; Li et al. 2011), narrower arteriolar diameters (Adar et al., 2010) and increased rates of ischemic stroke (Regan et al. 2006; Wellenius et al. 2012).

Our study has some limitations. First, outcome misclassification is a potential concern. We defined as our outcomes of interest the first hospital admission due to PD, AD or dementia. Hospital admissions, however, might be recorded with misclassification. A validation study of PD hospital discharges in Denmark, for instance, observed that approximately 82% of the reported PD admissions were accurate (Wermuth et al. 2012). We would expect any resulting bias, however, to be towards the null.

Exposure measurement error is also likely and, if present, it has also been shown to bias results towards the null (Kioumourtzoglou et al. 2014c). Furthermore, it is likely that mobility and/or

memory issues during the early stages of these conditions might decrease the amount of time spent outdoors, which could further bias the effect estimates towards the null. Given the average age of Medicare enrollees, nonetheless, mobility issues among non-cases is also likely (Kannus et al. 1996; Melton 1996).

Additionally, Medicare is an open cohort, in which subjects enter when they become 65 years old. Given no prior information on their health status, some subjects could have been hospitalized for the outcome of interest before becoming 65 years old. To examine whether their inclusion in our analyses affected our estimates, we conducted a sensitivity analysis excluding potentially prevalent cases and showed that our results were robust.

We detected significant effect heterogeneity in the estimates across cities for all outcomes. This could be partially attributed to the large number of cities and participants in our study, which provides ample power to detect heterogeneity even across the smallest differences in estimates. It is also likely that there are other factors contributing to this heterogeneity. For example, particle composition has been shown to modify the association between long-term exposures to air pollution and other outcomes, such as mortality (Kioumourtzoglou et al. 2014a). It should be noted, nevertheless, that the majority of the estimates across cities are positive and many of them significantly so (Figures 2-4), indicating that this heterogeneity only reflects differences across harmful estimates.

Finally, although residual confounding cannot be excluded, it is not likely in our study. Individual-level potential confounders, such as smoking and other life-style factors, are not available for Medicare enrollees, as these data are collected largely for utilization and cost statistics and not for epidemiological analyses. We have, however, selected a study design that

does not allow potential confounders varying across cities, or long-term trends, to affect our estimates. Moreover, we have adjusted for age, race, gender and SES, as well as any prior cardiopulmonary admission and severity of disease. In addition, chronic $PM_{2.5}$-mortality studies using Medicare data have yielded very similar results to studies adjusting for more individual-level confounders (Eftim et al. 2008; Zeger et al. 2008).

To our knowledge, this has been the first large-scale, multi-site epidemiologic study to examine the association between air pollution and admissions due to the two most common neurodegenerative diseases. We observed statistically significant, positive associations between long-term $PM_{2.5}$ city-wide exposures and PD, AD and dementia, in agreement with our hypothesis. In light of our limitations, our results should be viewed as preliminary; our findings provide the basis for further exploration in large epidemiologic studies with validated outcomes and more detailed information on potential individual-level confounders. Such studies are of crucial importance, as the implications for public health are tremendous, especially given the anticipated increase in life expectancy.

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Table 1. Number of subjects, cause-specific admissions and estimated hazard ratios (as HR (95%CI)) for Parkinson's Disease (PD), Alzheimer's Disease (AD) and dementia.

Results	**PD**	**AD**	**Dementia**
Main Analysis			
Total Population	9,817,806	9,817,806	9,817,806
# Admissions	119,425	266,725	203,463
HR (95%CI) per 1 μg/m^3	1.08 (1.04, 1.12)	1.15 (1.11, 1.19)	1.08 (1.05, 1.11)
HR (95%CI) per 5 μg/m^3	1.44 (1.22, 1.70)	2.00 (1.70, 2.35)	1.46 (1.29, 1.66)
Excluding cases in the first two years after enrollment			
Total Population[a]	8,011,978	7,976,136	7,897,538
# Admissions	80,788	202,614	143,888
HR (95%CI) per 1 μg/m^3	1.07 (1.03, 1.11)	1.15 (1.10, 1.19)	1.07 (1.04, 1.11)

[a]The number of total subjects for this sensitivity analysis is different by outcome, depending on the number of excluded cases in the first two years of follow-up by outcome.

Figure Legends

Figure 1. Map of the 50 cities included in our analyses. The size of the circles represents the size of population above 65 years living in each city (Census 2000) and the color the average $PM_{2.5}$ concentrations ($\mu g/m^3$).

Figure 2. City-specific $PM_{2.5}$ effect estimates on PD admissions, presented as log(HR) (95%CI) per 1 $\mu g/m^3$ increase in $PM_{2.5}$. The size of the symbol used for the effect estimate is proportional to its precision.

Figure 3. City-specific $PM_{2.5}$ effect estimates on AD admissions, presented as log(HR) (95%CI) per 1 $\mu g/m^3$ increase in $PM_{2.5}$. The size of the symbol used for the effect estimate is proportional to its precision.

Figure 4. City-specific $PM_{2.5}$ effect estimates on dementia admissions, presented as log(HR) (95%CI) per 1 $\mu g/m^3$ increase in $PM_{2.5}$. The size of the symbol used for the effect estimate is proportional to its precision.

Figure 1.

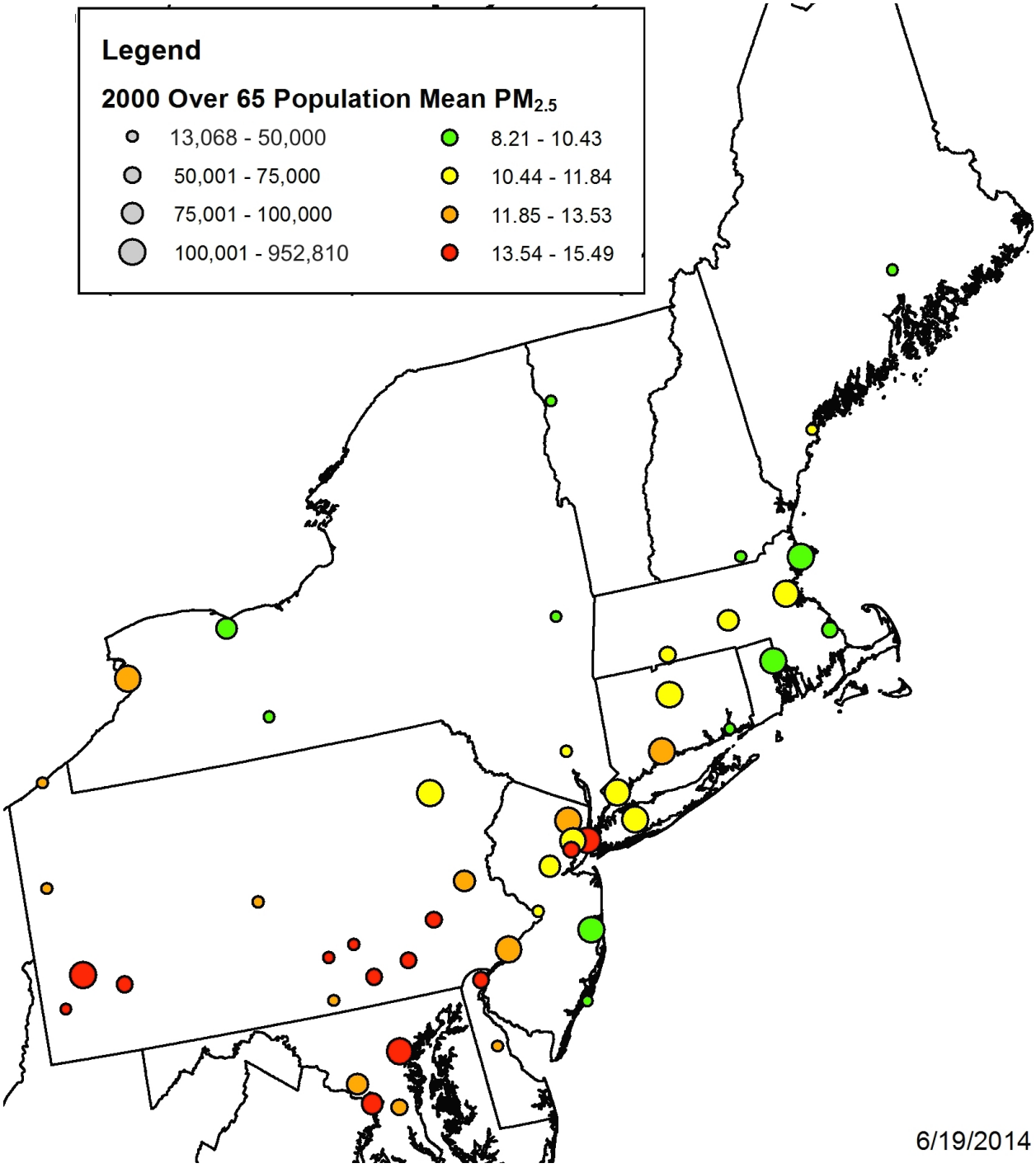

Legend
2000 Over 65 Population Mean PM2.5
13,068 - 50,000
50,001 - 75,000
75,001 - 100,000
100,001 - 952,810
8.21 - 10.43
10.44 - 11.84
11.85 - 13.53
13.54 - 15.49
6/19/2014

Figure 2.

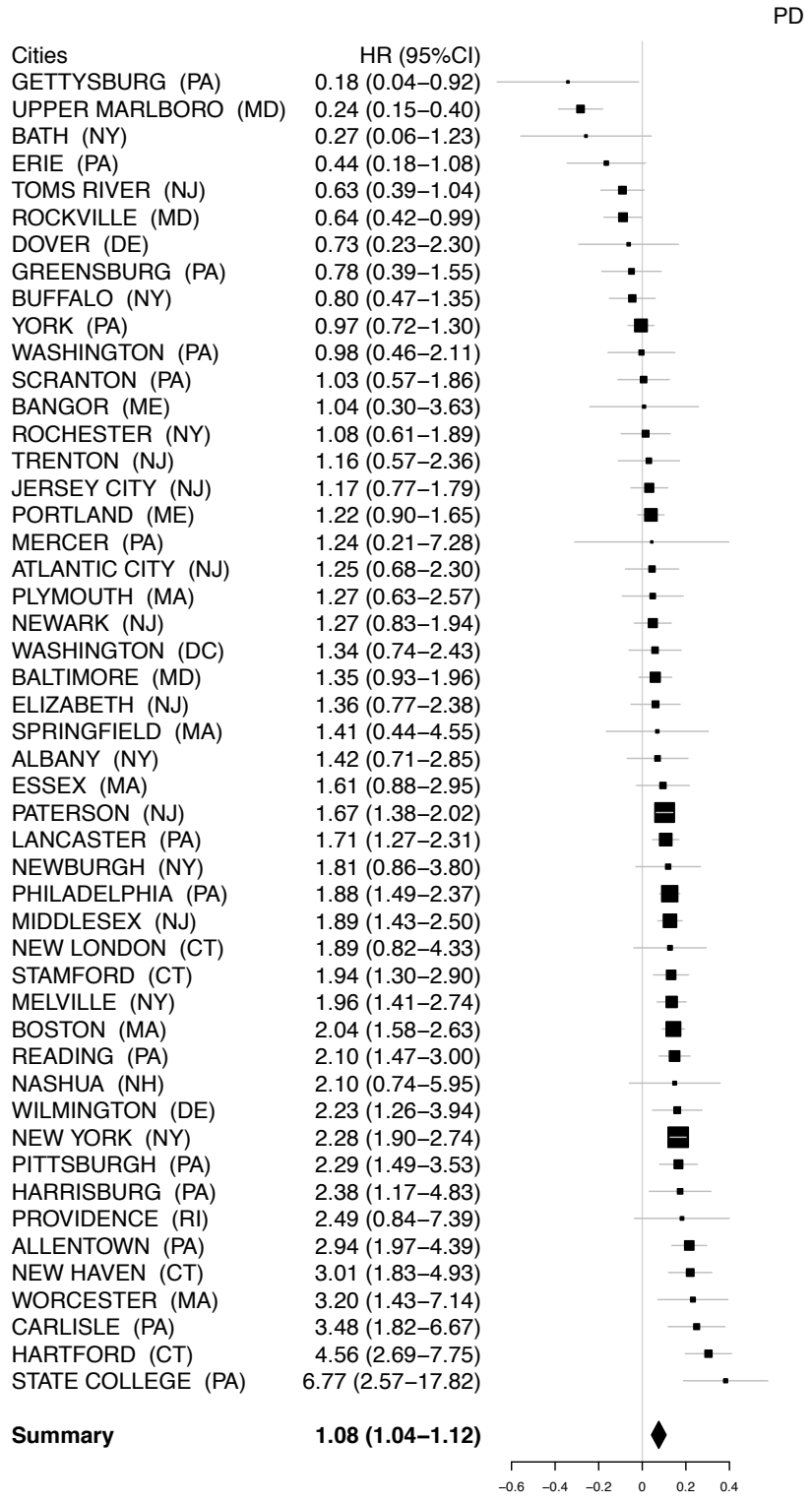

PD
Cities
HR (95%CI)
GETTYSBURG (PA) 0.18 (0.04–0.92)
UPPER MARLBORO (MD) 0.24 (0.15–0.40)
BATH (NY) 0.27 (0.06–1.23)
ERIE (PA) 0.44 (0.18–1.08)
TOMS RIVER (NJ) 0.63 (0.39–1.04)
ROCKVILLE (MD) 0.64 (0.42–0.99)
DOVER (DE) 0.73 (0.23–2.30)
GREENSBURG (PA) 0.78 (0.39–1.55)
BUFFALO (NY) 0.80 (0.47–1.35)
YORK (PA) 0.97 (0.72–1.30)
WASHINGTON (PA) 0.98 (0.46–2.11)
SCRANTON (PA) 1.03 (0.57–1.86)
BANGOR (ME) 1.04 (0.30–3.63)
ROCHESTER (NY) 1.08 (0.61–1.89)
TRENTON (NJ) 1.16 (0.57–2.36)
JERSEY CITY (NJ) 1.17 (0.77–1.79)
PORTLAND (ME) 1.22 (0.90–1.65)
MERCER (PA) 1.24 (0.21–7.28)
ATLANTIC CITY (NJ) 1.25 (0.68–2.30)
PLYMOUTH (MA) 1.27 (0.63–2.57)
NEWARK (NJ) 1.27 (0.83–1.94)
WASHINGTON (DC) 1.34 (0.74–2.43)
BALTIMORE (MD) 1.35 (0.93–1.96)
ELIZABETH (NJ) 1.36 (0.77–2.38)
SPRINGFIELD (MA) 1.41 (0.44–4.55)
ALBANY (NY) 1.42 (0.71–2.85)
ESSEX (MA) 1.61 (0.88–2.95)
PATERSON (NJ) 1.67 (1.38–2.02)
LANCASTER (PA) 1.71 (1.27–2.31)
NEWBURGH (NY) 1.81 (0.86–3.80)
PHILADELPHIA (PA) 1.88 (1.49–2.37)
MIDDLESEX (NJ) 1.89 (1.43–2.50)
NEW LONDON (CT) 1.89 (0.82–4.33)
STAMFORD (CT) 1.94 (1.30–2.90)
MELVILLE (NY) 1.96 (1.41–2.74)
BOSTON (MA) 2.04 (1.58–2.63)
READING (PA) 2.10 (1.47–3.00)
NASHUA (NH) 2.10 (0.74–5.95)
WILMINGTON (DE) 2.23 (1.26–3.94)
NEW YORK (NY) 2.28 (1.90–2.74)
PITTSBURGH (PA) 2.29 (1.49–3.53)
HARRISBURG (PA) 2.38 (1.17–4.83)
PROVIDENCE (RI) 2.49 (0.84–7.39)
ALLENTOWN (PA) 2.94 (1.97–4.39)
NEW HAVEN (CT) 3.01 (1.83–4.93)
WORCESTER (MA) 3.20 (1.43–7.14)
CARLISLE (PA) 3.48 (1.82–6.67)
HARTFORD (CT) 4.56 (2.69–7.75)
STATE COLLEGE (PA) 6.77 (2.57–17.82)
Summary **1.08 (1.04–1.12)**
−0.6 −0.4 −0.2 0 0.2 0.4

Figure 3.

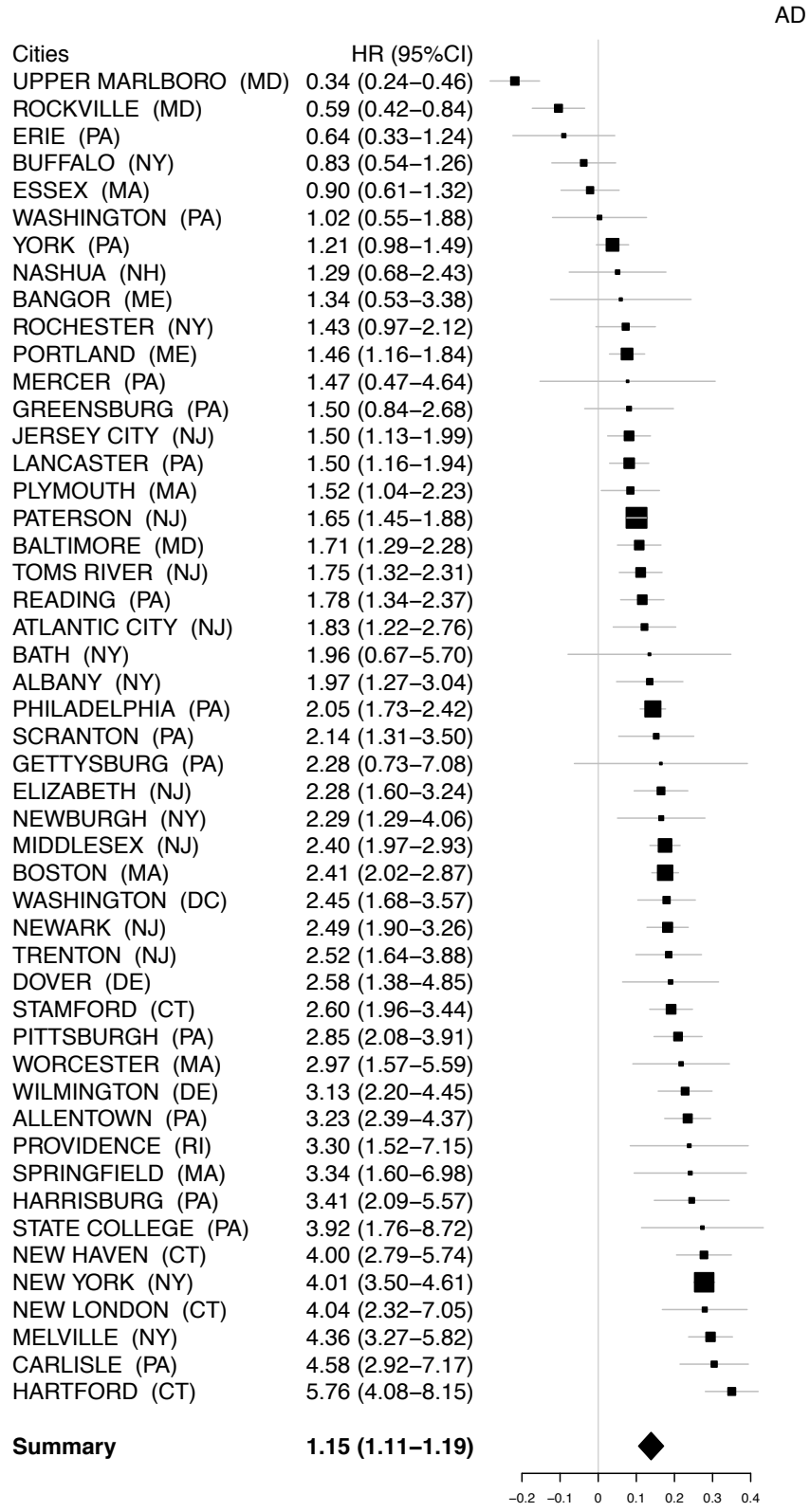
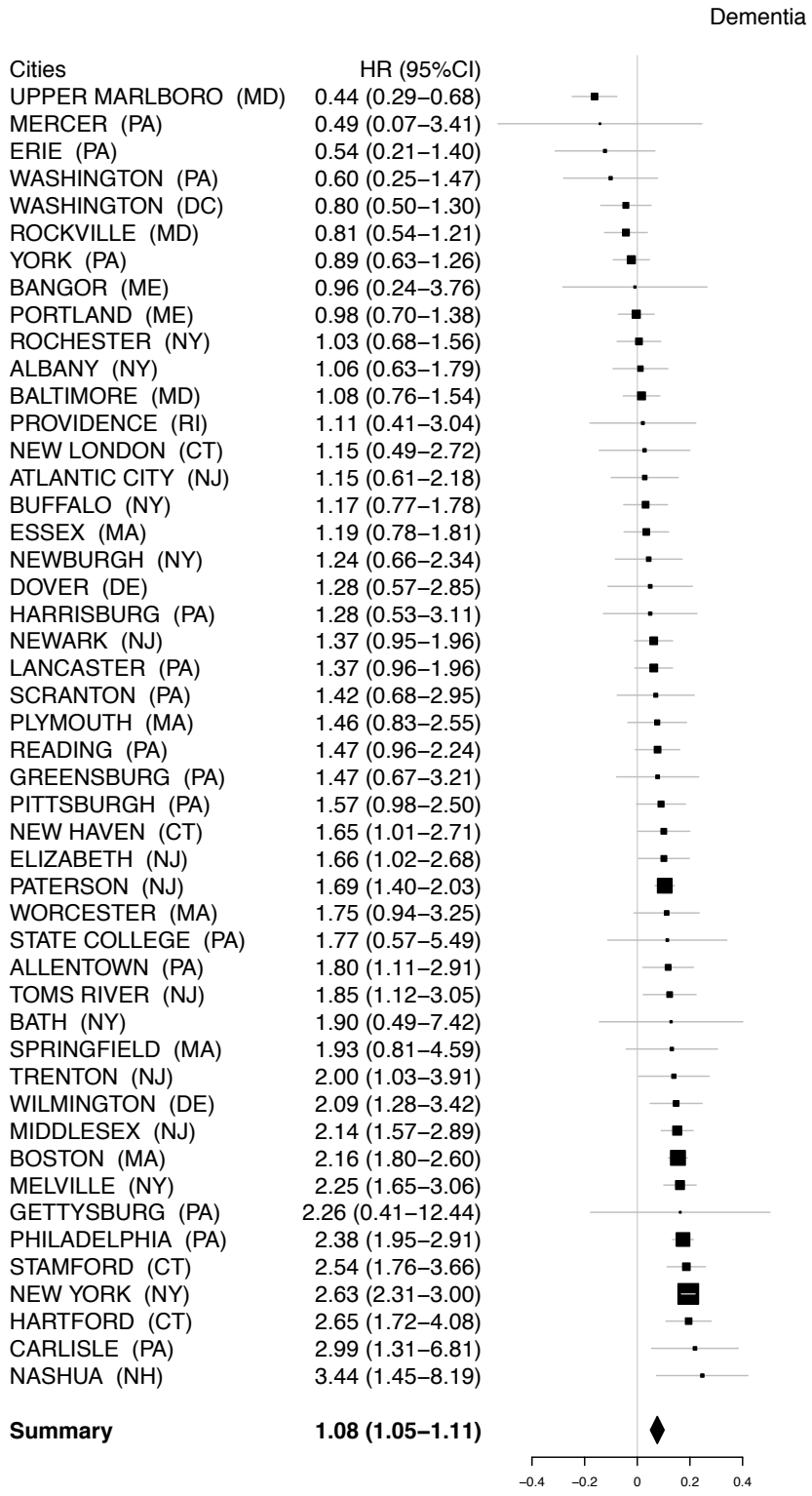

AD
Cities
HR (95%CI)
UPPER MARLBORO (MD) 0.34 (0.24–0.46)
ROCKVILLE (MD) 0.59 (0.42–0.84)
ERIE (PA) 0.64 (0.33–1.24)
BUFFALO (NY) 0.83 (0.54–1.26)
ESSEX (MA) 0.90 (0.61–1.32)
WASHINGTON (PA) 1.02 (0.55–1.88)
YORK (PA) 1.21 (0.98–1.49)
NASHUA (NH) 1.29 (0.68–2.43)
BANGOR (ME) 1.34 (0.53–3.38)
ROCHESTER (NY) 1.43 (0.97–2.12)
PORTLAND (ME) 1.46 (1.16–1.84)
MERCER (PA) 1.47 (0.47–4.64)
GREENSBURG (PA) 1.50 (0.84–2.68)
JERSEY CITY (NJ) 1.50 (1.13–1.99)
LANCASTER (PA) 1.50 (1.16–1.94)
PLYMOUTH (MA) 1.52 (1.04–2.23)
PATERSON (NJ) 1.65 (1.45–1.88)
BALTIMORE (MD) 1.71 (1.29–2.28)
TOMS RIVER (NJ) 1.75 (1.32–2.31)
READING (PA) 1.78 (1.34–2.37)
ATLANTIC CITY (NJ) 1.83 (1.22–2.76)
BATH (NY) 1.96 (0.67–5.70)
ALBANY (NY) 1.97 (1.27–3.04)
PHILADELPHIA (PA) 2.05 (1.73–2.42)
SCRANTON (PA) 2.14 (1.31–3.50)
GETTYSBURG (PA) 2.28 (0.73–7.08)
ELIZABETH (NJ) 2.28 (1.60–3.24)
NEWBURGH (NY) 2.29 (1.29–4.06)
MIDDLESEX (NJ) 2.40 (1.97–2.93)
BOSTON (MA) 2.41 (2.02–2.87)
WASHINGTON (DC) 2.45 (1.68–3.57)
NEWARK (NJ) 2.49 (1.90–3.26)
TRENTON (NJ) 2.52 (1.64–3.88)
DOVER (DE) 2.58 (1.38–4.85)
STAMFORD (CT) 2.60 (1.96–3.44)
PITTSBURGH (PA) 2.85 (2.08–3.91)
WORCESTER (MA) 2.97 (1.57–5.59)
WILMINGTON (DE) 3.13 (2.20–4.45)
ALLENTOWN (PA) 3.23 (2.39–4.37)
PROVIDENCE (RI) 3.30 (1.52–7.15)
SPRINGFIELD (MA) 3.34 (1.60–6.98)
HARRISBURG (PA) 3.41 (2.09–5.57)
STATE COLLEGE (PA) 3.92 (1.76–8.72)
NEW HAVEN (CT) 4.00 (2.79–5.74)
NEW YORK (NY) 4.01 (3.50–4.61)
NEW LONDON (CT) 4.04 (2.32–7.05)
MELVILLE (NY) 4.36 (3.27–5.82)
CARLISLE (PA) 4.58 (2.92–7.17)
HARTFORD (CT) 5.76 (4.08–8.15)
Summary **1.15 (1.11–1.19)**
–0.2 –0.1 0 0.1 0.2 0.3 0.4

Figure 4.


Dementia
Cities
HR (95%CI)
UPPER MARLBORO (MD) 0.44 (0.29–0.68)
MERCER (PA) 0.49 (0.07–3.41)
ERIE (PA) 0.54 (0.21–1.40)
WASHINGTON (PA) 0.60 (0.25–1.47)
WASHINGTON (DC) 0.80 (0.50–1.30)
ROCKVILLE (MD) 0.81 (0.54–1.21)
YORK (PA) 0.89 (0.63–1.26)
BANGOR (ME) 0.96 (0.24–3.76)
PORTLAND (ME) 0.98 (0.70–1.38)
ROCHESTER (NY) 1.03 (0.68–1.56)
ALBANY (NY) 1.06 (0.63–1.79)
BALTIMORE (MD) 1.08 (0.76–1.54)
PROVIDENCE (RI) 1.11 (0.41–3.04)
NEW LONDON (CT) 1.15 (0.49–2.72)
ATLANTIC CITY (NJ) 1.15 (0.61–2.18)
BUFFALO (NY) 1.17 (0.77–1.78)
ESSEX (MA) 1.19 (0.78–1.81)
NEWBURGH (NY) 1.24 (0.66–2.34)
DOVER (DE) 1.28 (0.57–2.85)
HARRISBURG (PA) 1.28 (0.53–3.11)
NEWARK (NJ) 1.37 (0.95–1.96)
LANCASTER (PA) 1.37 (0.96–1.96)
SCRANTON (PA) 1.42 (0.68–2.95)
PLYMOUTH (MA) 1.46 (0.83–2.55)
READING (PA) 1.47 (0.96–2.24)
GREENSBURG (PA) 1.47 (0.67–3.21)
PITTSBURGH (PA) 1.57 (0.98–2.50)
NEW HAVEN (CT) 1.65 (1.01–2.71)
ELIZABETH (NJ) 1.66 (1.02–2.68)
PATERSON (NJ) 1.69 (1.40–2.03)
WORCESTER (MA) 1.75 (0.94–3.25)
STATE COLLEGE (PA) 1.77 (0.57–5.49)
ALLENTOWN (PA) 1.80 (1.11–2.91)
TOMS RIVER (NJ) 1.85 (1.12–3.05)
BATH (NY) 1.90 (0.49–7.42)
SPRINGFIELD (MA) 1.93 (0.81–4.59)
TRENTON (NJ) 2.00 (1.03–3.91)
WILMINGTON (DE) 2.09 (1.28–3.42)
MIDDLESEX (NJ) 2.14 (1.57–2.89)
BOSTON (MA) 2.16 (1.80–2.60)
MELVILLE (NY) 2.25 (1.65–3.06)
GETTYSBURG (PA) 2.26 (0.41–12.44)
PHILADELPHIA (PA) 2.38 (1.95–2.91)
STAMFORD (CT) 2.54 (1.76–3.66)
NEW YORK (NY) 2.63 (2.31–3.00)
HARTFORD (CT) 2.65 (1.72–4.08)
CARLISLE (PA) 2.99 (1.31–6.81)
NASHUA (NH) 3.44 (1.45–8.19)
Summary **1.08 (1.05–1.11)**
−0.4
−0.2
0
0.2
0.4